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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/825,105	04/03/2001	Michael W. Russell	D6321	3233

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EXAMINER	
LI, QIAN J	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/825,105	Applicant(s) RUSSELL ET AL.	
	Examiner Janice Li	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *9-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 24-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☒ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group II, claims 1-8, 24-29, in Paper No. 5 is acknowledged. Claims 1-29 are pending, however, claims 9-23 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 5.

Claims 1-8, and 24-29 are under current examination.

Priority

This application claims the benefit of priority from US provisional application 60/194,498, filed 4/3/2000.

Claim Objections

Claims 1, 24, and 27 are objected to because of the following informalities: "a" is missing before "DNA sequence" in steps c) and d). Appropriate correction is required.

Claims 1, 24, and 27 are objected to because of the claim recitation, "a recombinant immunogen expressed from a plasmid", which embraces two distinct inventions, i.e. a method comprising administrating a plasmid expressing a recombinant immunogen (a nucleic acid); and a method comprising administrating a recombinant immunogen or a recombinant bacteria secreting the immunogen (a polypeptide); and.

Applicants have elected group II, drawn to administering an immunogen, for examination in the current application, therefore, the claims should be amended so that it clearly reads on the elected invention.

Claim 24 is objected to because "of" is missing from between "protein" and "an antigen" in line 6.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-8 and 24-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Toida et al* (Infect Immunity 1997;65:909-15), in view of *Rappuoli et al* (Immunol Today 1999 Nov;20:493-500), and further in view of *Schodel et al* (Infect Immunity 1989;57:1347-50; and Vaccine 1990;8:569-72) and *Connell et al* (Immunol Lett 1998;62:117-20; and Infect Immunity 1992;60:1653-61).

The claims are directed to a method of inducing immune response by administering a recombinant immunogen, preferably a salivary binding protein (SBR), wherein the enterotoxin is *E. coli* LT-IIa and LTIIb, wherein the immunogen is produced by expressing a plasmid comprising in operable linkage: an origin of replication, a promoter, a DNA sequence encoding a fusion protein of an antigen and subunits A2 and B of a type II heat-labile enterotoxin (LT-IIA2/B), wherein said plasmid is pVAR9, or

pSBR-LT-IIbA2/B, wherein the route of administration is selected from the group consisting of oral, intranasal, intrarectal, intravaginal, intramuscular, transcutaneous, and subcutaneous, wherein the immune response results in the production of antibodies in a bodily fluid, wherein the immune response is an antigen-specific T cell response, a cytotoxic T cell response, a Th1-type response, or an immunological tolerance.

Toida et al teach a method of inducing immune response by administering intragastrically a chimeric protein (a fusion immunogen) comprising SBR-CTA2/B (A2 and B subunits of cholera toxin, abstract), wherein the immunization induces antibodies in the serum (fig. 1), and T cell response, CD4+, and CD8+ (cytotoxic T cell) cells (fig. 3). *Toida et al* teach that immunization with SBR immunogen alone would induce a Th1-type of immune response, whereas SBR-CTA2/B skewed the cytokine expression pattern in PP and MLN cells toward Th2 type response (tab. 1). *Toida et al* do not teach LT-IIA2/B.

Rappuoli et al teach that both *E. coli* heat-labile enterotoxin and cholera toxin are potent mucosal immunogens and adjuvants in animal models (abstract). The subunits A1, A2, and B of an enterotoxin have different functions. The differences between CT and LT include different binding receptors (left column, page 495) and different types of immune response stimulated (left column, page 499). CT mediated adjuvanticity is accompanied by a preferential activation of Th2 type CD4+ cell populations, whereas LT adjuvanticity do not discriminate between Th1 and Th2. *Rappuoli et al* further teach that the polarization (Th1 or Th2) of the immune response is determined by other factors such as route of immunization.

In fact, the effects of various subunits of both CT and LT have been extensively investigated in the relevant art for their adjuvanticity. For example, *Schodel et al* teach a method of inducing immune response by administering orally recombinant immunogen secreted from recombinant *Salmonella* strain transformed with a plasmid encoding an immunogen of interest (human or woodchuck hepatitis B virus surface and nucleocapsid antigens) fused with B subunit of *E. coli* heat-labile enterotoxin, which induced an antibody response in bodily fluids of mice. In a subsequent publication, *Schodel et al* observe T cell response to antigens in C57BL/10 mice (see abstract). *Schodel et al* use a plasmid comprising a promoter, an origin of replication, and a DNA sequence encoding a fusion protein comprising an antigen of interest fused in frame to a subunit B of type II heat-labile enterotoxin. *Schodel et al* do not teach using the subunit A of type II heat-labile enterotoxin.

Connell et al teach that heat-labile enterotoxins produced by *E. coli* and CT produced by *Vibrio cholerae* belong to a family of proteins that are related in structure and function. They compare the adjuvant effect of CT with LT-IIa mixed with an antigen of interest, fimbrillin, and concluded that LTIIa and CT are equally potent adjuvants in the rat model (fig. 2 and paragraph bridging pages 119-120). In another study, *Connell et al* compared different combinations of heat-labile enterotoxin from *E. coli* (tables 1, 2, 4), and concluded, "ALL HOMOLOGOUS AND HETEROLOGOUS COMBINATIONS OF A AND B POLYPEPTIDES FROM TYPE I AND TYPE II HEAT-LABILE ENTEROTOXINS ARE CAPABLE OF ASSEMBLING INTO ACTIVE HOLOTOXINS IN VIVO, ALTHOUGH NOT WITH EQUAL EFFICIENCY" (last paragraph).

Although none of the references use the particular plasmid, pVAR9 or pSBR-LT-IIA2/B, various plasmid vectors have been widely used in the pertinent art, and the recited features, a promoter, an origin of replication, and a DNA sequence encoding a fusion protein, are basic properties of almost all expression vectors.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Toida et al,* by simply substituting the A2/B subunit of CT with that of LT, selecting a vector of interest and an antigen of interest as taught by *Rappuoli et al*, *Schodel et al, and Connell et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the method for inducing a non-Th2 type of response and whenever in need of targeting different type of receptors. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-8 and 24-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Russell et al* (US 6,030, 624), in view of *Rappuoli et al* (Immunol Today 1999 Nov;20:493-500), and further in view of *Schodel et al* (Infect Immunity 1989;57:1347-50; and Vaccine 1990;8:569-72) and *Connell et al* (Immunol Lett 1998;62:117-20; and Infect Immunity 1992;60:1653-61).

Russel et al teach a method of inducing an immune response by administering via oral or i.n. either a fusion immunogene of SBR-CT (cholera toxin, see example 1 in particular) or an attenuated strain of bacteria transformed with a plasmid encoding SBR-CTA2/B and secreting the fusion immunogen SBR-CTA2/B (example 20), wherein the

immunization induced antibodies in the bodily fluids (examples 1 & 8 in particular), CD3+ (general T cells), CD4+, and CD8+ (cytotoxic T cell) cells (fig. 7 and example 16). *Russel et al* teach that SBR antigen (as well as other bacterial antigen) alone induced low proliferative responses and a mixed type 1 and type 2 helper T cell activity, whereas coupling SBR to CTA2/B skewed the response towards Th2 activity (column 20, lines 31-50). *Russel et al* further teach that CT from *Vibrio cholerae* are related to heat-labile enterotoxin from *E. coli* as effective mucosal adjuvants (column 1, lines 54-58, and column 22, lines 12-13). *Russel et al* do not teach that the type of immune response triggered by LT as adjuvant, nor use of pVAR9 or pSBR-LT-IIA2/B.

Rappuoli et al teach that both *E. coli* heat-labile enterotoxin and cholera toxin are potent mucosal immunogens and adjuvants in animal models (abstract). The subunits A1, A2, and B of CT and LT have different functions. The differences between CT and LT include binding of different receptors (left column, page 495) and different type of immune response stimulated (left column, page 499). CT mediated adjuvanticity appears to be accompanied by a preferential activation of Th2 type CD4+ cell population, whereas LT adjuvanticity do not discriminate between Th1 and Th2. *Rappuoli et al* further indicate that the polarization (Th1 or Th2) of the immune response is determined by other factors such as antigen and route of immunization.

In fact, the effects of various subunits of both CT and LT have been extensively investigated in the relevant art for their adjuvanticity. For example, *Schodel et al* teach a method of inducing immune response by administering orally recombinant immunogen secreted from recombinant *Salmonella* strain transformed with a plasmid encoding an

immunogen of interest (human or woodchuck hepatitis B virus surface and nucleocapsid antigens) fused with B subunit of *E. coli* heat-labile enterotoxin, which induced an antibody response in bodily fluids of mice; in a subsequent publication, *Schodel et al* observe T cell response to the antigens in C57BL/10 mice (see abstract). *Schodel et al* do not teach using the subunit A of type II heat-labile enterotoxin.

Connell et al teach that heat-labile enterotoxins produced by *E. coli* and CT produced by *Vibrio cholerae* belong to a family of proteins that are related in structure and function. They compare the adjuvant effect of CT with LT-IIa mixed with an antigen of interest, fimbrillin, and concluded that LTIIa and CT are equally potent adjuvants in the rat model (fig. 2 and paragraph bridging pages 119-120). In another study, *Connell et al* compared different combinations of heat-labile enterotoxin from *E. coli* (tables 1, 2, 4), and concluded, "ALL HOMOLOGOUS AND HETEROLOGOUS COMBINATIONS OF A AND B POLYPEPTIDES FROM TYPE I AND TYPE II HEAT-LABILE ENTEROTOXINS ARE CAPABLE OF ASSEMBLING INTO ACTIVE HOLOTOXINS IN VIVO, ALTHOUGH NOT WITH EQUAL EFFICIENCY" (last paragraph).

Although none of the references use the particular plasmid, pVAR9 or pSBR-LT-IIA2/B, various plasmid vectors have been widely used in the pertinent art, and the recited features, a promoter, an origin of replication, and a DNA sequence encoding a fusion protein, are basic properties of almost all expression vectors.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Russel et al,* by simply substituting the A2/B subunit of CT with that of LT, selecting a vector of interest and an antigen of interest as taught by *Rappuoli et al*, *Schodel et al, and Connell et al* with a

reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the method whenever in need of inducing a non-Th2 type of response and for targeting different type of receptors. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 6-8, and 24-29 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6,030,624, in view of *Rappuoli et al* (Immunol Today 1999 Nov;20:493-500), and further in view of *Schodel et al* (Infect Immunity 1989;57:1347-50; and Vaccine 1990;8:569-72) and *Connell et al* (Immunol Lett 1998;62:117-20; and Infect Immunity 1992;60:1653-61).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the present application and claims 1-9 of the cited patent are

each drawn to a method of inducing an immune response by administration of a recombinant immunogen or a recombinant bacteria expressing an immunogen. *Russel et al* further teach that CT could skew T cell response toward a Th2 type and CT from *Vibrio cholerae* are related to heat-labile enterotoxin from *E. coli* as effective mucosal adjuvants (column 1, lines 54-58, and column 22, lines 12-13).

The processes of the present application and the cited patent differ one from the other in that the cited patent does not teach that LT-IIA2/B adjuvant do not discriminate between Th1 or Th2 response, thus when combined with a bacterial antigen or the like, could enhance a Th1 response.

However, before the effective filing date of the instant application, *Rappuoli et al* teach that both *E. coli* heat-labile enterotoxin and cholera toxin are potent mucosal immunogens and adjuvants in animal models (abstract), that the differences between CT and LT include binding of different receptors (left column, page 495) and stimulating different type of immune response (left column, page 499). CT mediated adjuvanticity appears to be accompanied by a preferential activation of Th2 type CD4+ cell population, whereas LT adjuvanticity do not discriminate between Th1 and Th2.

In fact, the effects of various subunits of both CT and LT have been extensively investigated in the relevant art for their adjuvanticity. For example, *Schodel et al* teach a method of inducing immune response by administering orally recombinant immunogen secreted from recombinant *Salmonella* strain transformed with a plasmid encoding an immunogen of interest (human or woodchuck hepatitis B virus surface and nucleocapsid antigens) fused with B subunit of *E. coli* heat-labile enterotoxin, which induced an

antibody response in bodily fluids of mice; in a subsequent publication, *Schodel et al* observe T cell response to the antigens in C57BL/10 mice (see abstract). *Schodel et al* do not teach using the subunit A of type II heat-labile enterotoxin.

Connell et al teach that heat-labile enterotoxins produced by *E. coli* and CT produced by *Vibrio cholerae* belong to a family of proteins that are related in structure and function. They compare the adjuvant effect of CT with LT-IIa mixed with an antigen of interest, fimbrillin, and concluded that LTIIa and CT are equally potent adjuvants in the rat model (fig. 2 and paragraph bridging pages 119-120). In another study, *Connell et al* compared different combinations of heat-labile enterotoxin from *E. coli* (tables 1, 2, 4), and concluded, "ALL HOMOLOGOUS AND HETEROLOGOUS COMBINATIONS OF A AND B POLYPEPTIDES FROM TYPE I AND TYPE II HEAT-LABILE ENTEROTOXINS ARE CAPABLE OF ASSEMBLING INTO ACTIVE HOLOTOXINS IN VIVO, ALTHOUGH NOT WITH EQUAL EFFICIENCY" (last paragraph).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Russel et al,* by simply substituting the A2/B subunit of CT with that of LT as taught by *Rappuoli et al, Schodel et al, and Connell et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the method whenever in need of inducing a non-Th2 type of response and for targeting different type of receptors. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Accordingly, the claimed processes in the cited patent and the present application are obvious variants.

Therefore, the inventions as claimed are co-extensive.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
August 19, 2002

JAMES KETTER
PRIMARY EXAMINER